"endothelial cells." Claim 11 has been amended to correct an obvious spelling error. Claim 12 has been amended to correct antecedent basis for "A2B adenosine receptor." Claim 14 has been amended to correct antecedent basis for "antagonist." None of these amendments are made to narrow the scope the claims. Rather, the amendments are made to clarify the claims. No new matter is added by these amendments.

The Rejection of Claims 1-15 Under 35 U.S.C. §112, second paragraph

Claims 1-15 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

The claims have been amended and are definite. Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 1-6 and 9-15 Under 35 U.S.C. §112, first paragraph

Claims 1-15 stand rejected under 35 U.S.C. §112, second paragraph as allegedly lacking enablement. Applicants have provided a separate argument for claims 7 and 8 below. Applicants respectfully traverse the rejection as it applies to claims 1-6 and 9-15.

Claims 1-6 and 9-15 recite methods for inhibiting the proliferation of mammalian cells that express an A_{2B} adenosine receptor comprising administering a therapeutically effective amount of an A_{2B} adenosine receptor antagonist to the mammalian cells. The A_{2B} adenosine receptor antagonist can be, for example, a non-selective or selective adenosine receptor antagonist.

The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01. "The determination of

what constitutes undue experimentation is a given case requires the application of a standard of reasonableness, having due regard of the nature of the invention and the state of the art." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Ansul Co. v. Uniroyal, Inc.*, 169 U.S.P.Q. 759, 762-63 (2d Cir. 1971). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*

The Office Action recognizes that the specification is enabling for the design and administration of A_{2B} antagonists to cells in culture, however, the Office Action asserts that the specification is not enabled for the design and administration of A_{2B} antagonists to cells in a whole organisms with an expectation of success. The Office Action asserts mammals are known to differ in their physiology so that success of a drug in one whole organism does not necessarily correlate to success of the same drug in another whole organism. Factors such as toxicity of the compound, stability *in vivo*, routes of administration and target specificity/availability can vary greatly according to the Office Action. The Office Action concludes that there is no guidance in the specification or the art to suggest that these compounds would function in a whole organism to inhibit proliferation of mammalian cells that express an A_{2B} adenosine receptor. The Office Action postulates that antagonism of all accessible A_{2B} receptors in whole organism could result in undesired side effects.

In contrast to the Office's allegation, the specification provides considerable guidance to enable a skilled artisan to make and use an A_{2B} adenosine receptor antagonist for inhibiting the proliferation of mammalian cells that express an A_{2B} adenosine receptor.

The Federal Circuit has found that data showing the successful use of compounds as antitumor substances in tumor model systems were sufficient to enable the use of those compounds as anticancer drugs in animals. *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). As established by the Federal Circuit, "if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate.*" *In re Brana*, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (emphasis added); M.P.E.P.§ 2164.02.

One of ordinary skill in the art would recognize that appropriate model cell cultures, such as the human retinal endothelial cells used in the working examples of the instant application, could be used as a predictive model for *in vivo* activity. The Office Action has not provided evidence that a human retinal endothelial cell models, as used in the working examples of the instant application, do not correlate with inhibition of cell proliferation in mammals. The Office Action has only provided general bald assertions that do not address the model used in the working examples. Absent evidence to the contrary, the Examiner must provide evidence that the cell model systems used in the application correlates to cell proliferation.

The Office Action asserts that neither the specification nor the art address design of pharmaceuticals that would enable one skilled in the art to successfully design A_{2B} drugs that are ready for *in vivo* use without a significant amount of trial and error experimentation common to the entire field of drug development. Initially, the *Brana* court stated that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id.* at 1442. Secondly, routine experimentation is permissible. *See In re Wands*, 8 U.S.P.Q.2d at 1404. The

specification teaches that the antagonists of the invention are useful to treat cell proliferation disorders mediated by an A_{2B} adenosine receptor and demonstrates with working examples the anti-proliferative effect of the antagonists in a recognized, correlative model and the Office Action has provided no evidence or reasoning as to why claims 1-6 and 9-15 are not enabled.

The Office Action asserts that there is no known formula for designing an antagonist with known *in vivo* function for specific therapeutic functions. The Office Action assets that specific agonists and antagonists were not known at the time the invention was made. However, the working examples clearly demonstrate that antagonists of A_{2B} receptors were known at the time the invention was made, including, for example, 3-N-propylxanthine, JW-V1-08, and xanthine amine congener. Secondly, as discussed above, A_{2B} receptor antagonists do not have to be "ready" for *in vivo* human use.

Using the guidance provided in the specification along with information known in the art, one skilled in the art would be able to synthesize and use A_{2B} receptor antagonists for inhibiting the proliferation of mammalian cells expressing an A_{2B} receptor in a variety of biological systems. Applicants clearly demonstrate that A_{2B} adenosine receptor agonists can inhibit the proliferation of mammalian cells *in vitro* (see Example 1). One of ordinary skill in the art would recognize that appropriate cell cultures, such as the human retinal endothelial cells used in the working examples of the instant application, could be used as a predictive model for *in vivo* anti-proliferative activity.

The specification is therefore fully enabling for claims 1-6 and 9-15, which can be readily practiced by one skilled in the art. The Office Action has failed to provide any evidence whatsoever that the invention recited in claims 1-6 and 9-15 would not work for its intended purpose. The Office Action has failed to establish a *prima facie* case of lack of enablement

because it has not provided any technical reasons and/or references to support its bald assertions. *See* M.P.E.P. §2164.04. Accordingly, Applicants respectfully request that the 35 U.S.C. § 112, first paragraph, rejection of claims 1-6 and 9-15 be withdrawn.

The Rejection of Claims 7-8 Under 35 U.S.C. §112, first paragraph

Claims 7-8 stand rejected under 35 U.S.C. §112, second paragraph as allegedly lacking enablement. Applicants have provided a separate arguments for claims 7 and 8 because the Office Action has provided a detailed rejection for these two claims. Applicants respectfully traverse the rejection.

Claims 7 and 8 recite methods for inhibiting the proliferation of mammalian cells that express an A_{2B} adenosine receptor comprising administering a therapeutically effective amount of an A_{2B} adenosine receptor antagonist to the mammalian cells, wherein the antagonist is an A_{2B} adenosine receptor antisense oligonucleotide or an A_{2B}-specific ribozyme.

The Office Action assets that the specification does not teach (1) stability of the an antisense or ribozyme molecule *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity and (4) entry of the molecule into the cell and effective action therein. The Office Action asserts that these factors are highly unpredictable in the art.

The Office Action cites several references to support its position that antisense and ribozyme therapy is an unpredicatable art. However, there is ample support in the art for the activity of these molecules in cell culture and animal model systems. For example, see: Flory *et al.* 1996, *Proc. Natl. Acad. Sci.* USA, 93, 754; Larsson *et al.*, 1994, *Nucleic Acid Res.* 22, 2242; Efrat *et al.*, 1994, *Proc. Natl. Acad. Sci.* USA, 91, 2051; Lyngstadaas *et al.*, 1995, *EMBO. J.* 14, 5224; Lieber and Kay, 1996, *J. Virol.* 70, 3153; Yamamoto *et al.*, 1996, *Int. J. Cancer,* 65, 519;

Sioud, 1996, *Eur. J. Immunol.* 26, 1026; Desjardins *et al.*, 1996, *J. Pharmacol. Exptl. Ther.* 278, 1419; Lewin *et al.*, 1998, *Nat. Med.* 4, 967; Sioud *et al.*, 1998, *Nat. Biotech.* 16, 557; Alami *et al.*, Blood Cells Mols. Dis., 1999, 25, 110; Frimerman *et al.*, 1999 Circulation, 99, 697; Tanabe *et al.*, 2000, Nature, 406, 473; Zhao *et al.*, 1998 Development, 125, 1899; Samarsky *et al.*, 1999, PNAS, 96, 6609;Macejack *et al.*, 1999, J. Virol., 73, 7745; Amado *et al.*, 1999 Hum. Gene. Ther., 10, 2255 Cameron et al., PNAS, 86:9139-9143 (1989) and in particular: Cushman *et al.*, 1996, "Ribozyme inhibition of VEGF-mediated endothelial cell proliferation in cell culture and VEGF-induced angiogenesis in rat corneal model" Abstract in IBC USA Conferences–Angiogenesis Inhibitors; Lewin *et al.*, 1998 *Nature Med.*, 4, 967; and Parry *et al.*, 1999 NAR, 27, 2569, which disclose molecules that are active in rat corneal and retinal models (copies attached).

The acceptance of the therapeutic use of ribozymes is further demonstrated by the FDA approval of an Investigational New Drug application for ribozyme inhibition of HIV (*see, e.g.*, Seachrist, *Bioworld Today*, Jan. 15, 1997, at 1) (copy attached). FDA approval in this case provides further confirmation that treatment with ribozymes is accepted by those skilled in the art as well as by regulatory authorities. The therapeutic use of ribozymes for the treatment of other diseases, in addition to those associated with HIV, would not require undue experimentation by those of ordinary skill in the art based on the guidance provided from the work done on HIV and on the wide variety of targets, cell types, and diseases described above.

The Federal Circuit clearly states that a patent need not teach, and preferably omits, that which is well known in the art. *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986); M.P.E.P. §2164.01. Given the teachings of the specification and the state of the art at the time of filing, one of skill in the art

would be able to design and use ribozymes or antisense molecules that target an A_{2B} adenosine receptor.

The Rejection of Claims 16-17 Under 35 U.S.C. § 102(a)

Claims 16-17 stand rejected under 35 U.S.C. § 102 (a) as allegedly anticipated by Grant *et al.* Applicants respectfully traverse the rejection.

The instant application claims priority to U.S. Provisional application 60/183,141 filed on February 17, 2000. The Grant reference is the Applicant's own disclosure of their work that was published less than a year before the priority date. Applicants' disclosure of their own work within the year before the application filing date cannot be used against them under 35 U.S.C. §102(a). *In re Katz*, 215 U.S.P.Q. 14 (CCPA 1982); M.P.E.P. §2131.05.

Affidavits are attached that have been signed by both of the inventors of the instant application. The affidavits make clear that the Grant reference is describing the Applicants' own work. Therefore, Grant is not an anticipating reference under 35 U.S.C. §102(a). Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 16-18 Under 35 U.S.C. § 103

Claims 16-18 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Grant *et al.* and Kvanta *et al.* in view of Kemp *et al.*, Kim *et al.*, and Klotz *et al.* Applicants respectfully traverse the rejection.

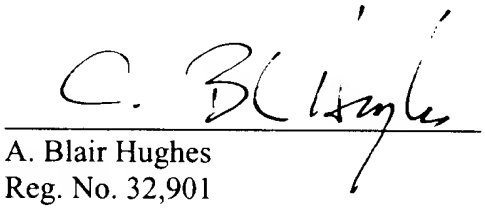
Claims 16-18 recite methods for assaying compounds to determine if they are A_{2B} adenosine receptor agonists or antagonists and compounds identified by the methods. The method comprises adding test compounds to first and second sample of human retinal endothelial cells and comparing the number of new cells in each sample.

As discussed above, Grant is not prior art to this application. Therefore, it can not be considered as a primary reference in this rejection. Kvanta is relied upon by the Office to demonstrate a motivation for further study of the role of adenosine receptors in the rat retina. Kim, Klotz, and Kemp are relied upon by the Office to show motivation for design of novel agonists and antagonists to an A_{2B} receptor. Kvanta in view of Kim, Klotz and Kemp do not teach or suggest a method of human retinal endothelial cell assay for identification of A_{2B} antagonists and agonists. Neither does the Office Action allege that this combination of references teach or suggest such an assay.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

Date: May 6, 2002

By: 

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